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Perspective

Linkage Pathways of DNA–Nanoparticle Conjugates and Biological Applications

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Abstract: DNA–nanoparticle conjugates have extraordinary optical and catalytic properties that have attracted great interest in biosensing and biomedical applications. Combining these special qualities has made it possible to create extremely sensitive and selective biomolecule detection methods, as well as effective nanopharmaceutical carriers and therapy medications. In particular, inorganic nanoparticles, such as metal nanoparticles, metal–organic framework nanoparticles, or upconversion nanoparticles with relatively inert surfaces can easily bind to DNA through covalent bonds, ligand bonds, electrostatic adsorption, biotin–streptavidin interactions and click chemistry to form DNA–nanoparticle conjugates for a broad range of applications in biosensing and biomedicine due to their exceptional surface modifiability. In this review, we summarize the recent advances in the assembly mechanism of DNA–nanoparticle conjugates and their biological applications. The challenges of designing DNA–nanoparticle conjugates and their further applications are also discussed.

Keywords: DNA; inorganic nanoparticles; biosensing; biomedical

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1. Introduction

With its simple structure and complicated functions, DNA is a crucial building block in the creation of the blueprint for life and is employed extensively in biosensing and biomedicine [1,2]. However, the instability of the DNA structure in living organisms limits the efficient performance of its functions. Therefore, the construction of nanoscale models by employing DNA as a building block for improving its stability has been widely studied [3,4]. Nevertheless, the high price of its assembly also restricts its application for a wide range of purposes. In the past decades, DNA nanotechnology has rapidly evolved from structural DNA nanotechnology alone to assembly DNA nanotechnology in order to propose more effective methods to enhance the stability of DNA applied in living organisms [5–7].

Among them, the assembly of DNA on the surface of nanomaterials as a carrier and changing the presence state of DNA from the solution phase to interfacial connection can be a promising approach to solve the confusion of DNA instability in living organisms [8,9]. Incorporating DNA molecules to decorate inorganic nanoscale components brings up new possibilities for creating nanoparticles with distinctive applications in the realms of biosensing and biomedical applications [10]. The flexibility and adaptability of DNA-based platforms allow for the construction of complex structures from nanoparticles utilizing DNA-programmable interparticle interactions [11,12]. To date, in order to further expand the fields of its application, the investigation stages for the functionalization of DNA on the surface of nanoparticles can be classified into the following aspects:

(1) Searching for diversely functional DNA sequences. The chemical activity of DNA grows into new areas outside of storing and transferring genetic information in the field of functional DNA nanotechnology. The two main representative categories of functional DNAs that are generated by in vitro selection with particular binding

affinities and catalytic capabilities are aptamers and DNAzymes [13,14]. Aptamers are chosen by a procedure called systematic evolution of ligands by exponential enrichment (SELEX), and the selection process has evolved from in vitro to in vivo. Aptamers are widely employed in the assembly of sensitive biosensors, the construction of bioimaging agents, and targeted therapeutics [15]. An additional category of valuable DNA molecules with catalytic activity is DNAzymes. RNA-cleaving DNAzymes are of particular fascination due to their quick reaction time and simplicity in application in life [16]. DNAzymes act by binding to specific metal ions as catalytic cofactors and are ideal for functionalized nanoparticle surfaces [17].

(2) Development of inorganic nanoparticles with facile modification of DNA on the surface. By adding DNA nanotechnology into nanoparticle research, precise geometric construction of nanoparticles and change in surface properties have been described [18,19]. The best candidates for carrying smart DNA walkers/motors, activatable aptamers, and DNAzyme-based systems that respond to stimuli for biosensing, bioimaging, and biomedical applications are nanoparticles with a substantial surface area, favorable biocompatibility, outstanding stability, and beneficial physical and chemical properties, such as gold nanoparticles (AuNPs), upconversion nanomaterials (UCNPs) and so on [20–22].

(3) Exploring the way DNA connects to nanoparticles. The facile modification properties of DNA encourage the interface engineering of nanoparticles based on several theories. Mirkin was the first to suggest that sulfurizing DNA and attaching it to AuNPs would result in the development of AuNPs-linked DNA [23,24]. The coordinated binding between DNA base structure and rare earth elements can also connect DNA to UCNPs [25–29]. The interface between DNA molecules and nanoparticles also involves additional covalent and noncovalent connecting techniques, such as the biotin-Streptavidin interaction and click chemistry [30,31]. Thereafter, electrostatic contact is another often employed technique for affixing DNA molecules to positively charged nanoparticles on the surface due to the negative charge of the phosphate backbone on the surface of the DNA structure [32]. Electrostatic interactions exist in various forms, such as hydrogen bonding, hydrophobic contacts, van der Waals forces, and ionic bonding, DNA–nanoparticle conjugates assembled with the above forms also demonstrate excellent stability and extremely promising applications. For instance, the mechanism of DNA's denaturation and rehybridization is employed to create hydrogen bonds between base pairs that are complementary on adjacent DNA strands, resulting in the formation of interconnected structures. Then, silicate nanodiscs are utilized to create extra network points by luring electrostatic interactions with the DNA backbone [33]. This improves the mechanical elasticity of the hydrogel formulation and achieves the release of the loaded drug dexamethasone, realizing the conjugate's ability to treat osteoporosis disease.

The functionalized connection of DNA on the surface of nanoparticles can not only stabilize DNA but also combine the unique physicochemical properties of nanoparticles themselves to realize the superposition function after the double unit compound (Figure 1). In recent years, the multifaceted applications of DNA–nanoparticle conjugates in biosensing and biomedicine are also summarized and introduced, but the articles focusing on the mode of connection between DNA and nanoparticles and thus summarizing the state-of-the-art of their applications in biosensing and biomedical have not yet been reported. Consequently, we outline many tried and true methods for DNA functionalization on various surface ligands and nanoparticles and provide a summary and overview of the biological applications of these methods over the past five years.

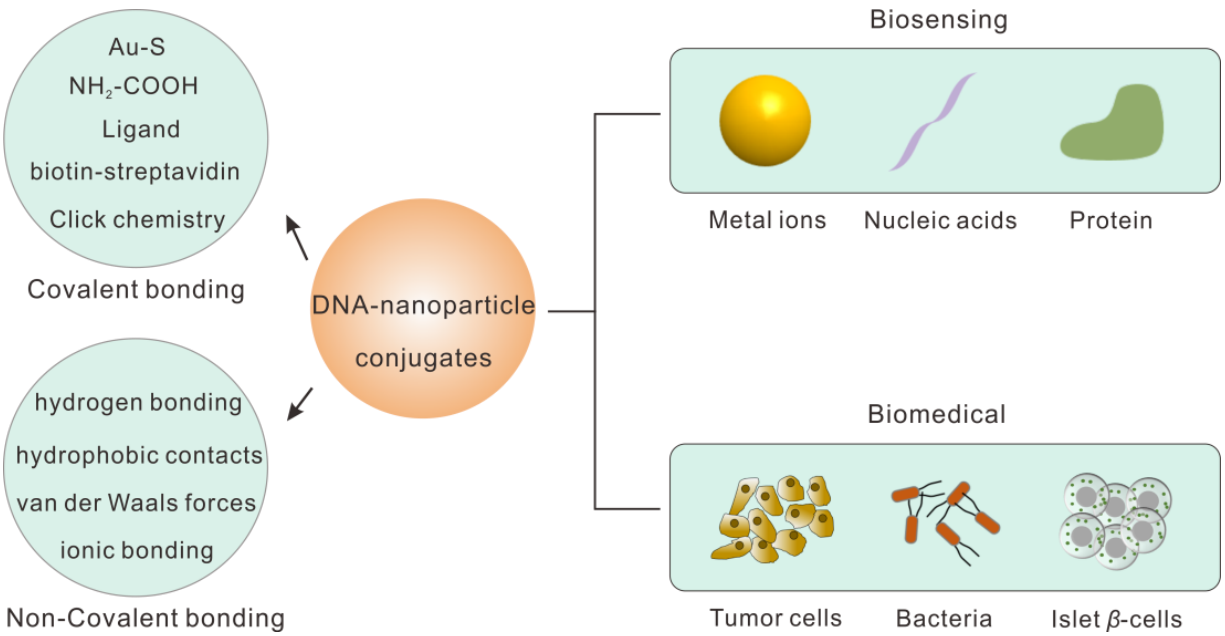

Figure 1. Schematic of the classes of DNA-conjugated nanoparticles and their applications.

2. DNA–Nanoparticle Conjugates Design

Fabricating the physico-chemical properties of inorganic nanoparticles with DNA attached to produce novel structures is particularly exciting because these materials' physico-chemical properties differ greatly from those of their bulk structure [34]. Their small size and high surface-to-volume ratio give rise to these novel features, which may be tailored by varying their chemical makeup, size, and shape [35]. The approaches employed to achieve this goal can be classified as top-down or bottom-up. In contrast to bottom-up approaches, which rely on the organization of building blocks (such as molecules, atoms, and nanoparticles) to form larger structures and have broader structural versatility, top-down approaches employ external sources to design nanoscale features on the surface of the body but are more expensive to synthesize [36].

In this section, we summarize several approaches for the bottom-up synthesis of DNA–nanoparticle conjugates, employing DNA as a linker and inorganic nanomaterials as structural units.

2.1. Covalent Bonding

Covalent bonding to nanoparticles by exploiting the chemical modifiability of DNA and the properties of the bases themselves is the key method of DNA–nanoparticle conjugate formation [12]. Among the chemically modified DNA, phosphorothioate DNA, amino-modified DNA, biotin-modified DNA, and alkyne or azide-modified DNA are the primary representatives.

The technique that is employed the most frequently is to modify DNA with -SH functional groups on the surface of plasma metal nanoparticles and then to ensure that DNA and nanoparticles contact closely by means of covalent metal–SH interactions [37]. It is worth noting that end-labeled thiol is the main anchor for linking DNA to AuNPs because of strong Au–thiol interactions. For example, SH-functionalized DNA sequences are covalently attached to the surface of AuNPs to construct a structurally stable thermal sensor for the highly sensitive in situ detection of exosomal miRNAs without RNA extraction or target amplification (Figure 2a) [38]. It has been demonstrated that DNA-functionalized gold nanoprobes linked by Au–sulfur bonds exhibit remarkable stability in exosomes, ensuring the proper operation of the sensing probes. This stable structure is also employed in a number of nanoprobes constructed based on this metal–SH bonding method [39]. However, another method of functionalizing DNA on the surface of AuNPs, namely

polyadenine (poly A) DNA functionalized AuNPs, has received increasing attention due to the high cost of thiols [40]. Metal ions can undergo coordination reactions with the amino acid side chains of adenine bases, thus completing the attachment of functionalized DNA strands to AuNPs. This more time-efficient method of conjugation can facilitate the further development of this method in the future for several applications [41].

Covalent cross-linking and phosphate group coordination are the two primary techniques for ligating functionalized DNA on the surface of UCNPs [42]. Covalent cross-linking is often accomplished by modifying functional molecules. For example, as shown in Figure 2b, transferring UCNPs from the organic phase to the aqueous phase and modifying the surface with functional modification of -COOH, covalent cross-linking can occur with the DNA strands with modified -NH_2 at the ends to generate -NH-CO- bond, thus realizing the functionalization of DNA on the surface of UCNPs [43]. In addition, Ln^{3+}-based UCNPs provide a surface rich in multiple functional groups through the coordination of Ln^{3+} with electron-rich groups, including -NH_2, -COOH, $SO_4{}^{2-}$, and phosphate group $PO_4{}^{3-}$. The phosphate group on the DNA backbone can easily replace -COOH because the coordination between $PO_4{}^{3-}$ and Ln^{3+} is stronger than that between -COOH and Ln^{3+}, enabling the coordination bonding between the DNA and UCNPs to complete the assembly of stable nanoprobes [44]. Biotin-modified DNA can be attached to the surface of nanoparticles by covalent bonds between biotin and streptavidin (biotin–avidin), which is also a connecting method for preparing stable nanosensor molecules (Figure 2c) [45–48]. The above two types of modification of functional molecules on nanoparticles can extend the forms of covalently attached DNA molecules and provide more possibilities for the formation of stable functionalized sensing probes.

Recently, the attachment of alkyne-modified DNA to the surface of nanoparticles utilizing a click reaction is extensively performed, which is based on a copper-catalyzed azide–alkyne cyclization reaction [49–51]. This is because the click reaction, which is a quick and effective chemical reaction, takes place in mild conditions and does not require a catalyst to produce a high yield of product. For example, a "click chemistry" approach allows for the preparation of stable Janus nanoparticles containing both PEG and azide–DNA to form AuNP dimers under target responders and conditions for in situ SERS detection and imaging analysis of cancer cells [52]. By adding an azide group and an alkyne group to the two DNA strands in order to bind the two AuNPs together, the efficiency of the assembly may also be guaranteed (Figure 2d) [53]. In addition to improving the stability of the probe, the high efficiency of click chemistry can be exploited to enhance the enrichment of DNA on the surface of nanoparticles, allowing further improvement of the sensing sensitivity of the target detectors [54]. For other nanoparticles, such as metal–organic framework (MOF) materials, DNA can also be attached to the surface of the nanoparticles by click chemistry, acting as a reaction switch for the target and further extending the biological applications of DNA–nanoparticle conjugates [55].

2.2. Non-Covalent Bonding

Hydrogen bonds, hydrophobic contacts, van der Waals forces, and ionic bonds are non-covalent bonds collectively known as electrostatic adsorption that can bring DNA closer to nanoparticles and form DNA–nanoparticle conjugates [56–58].

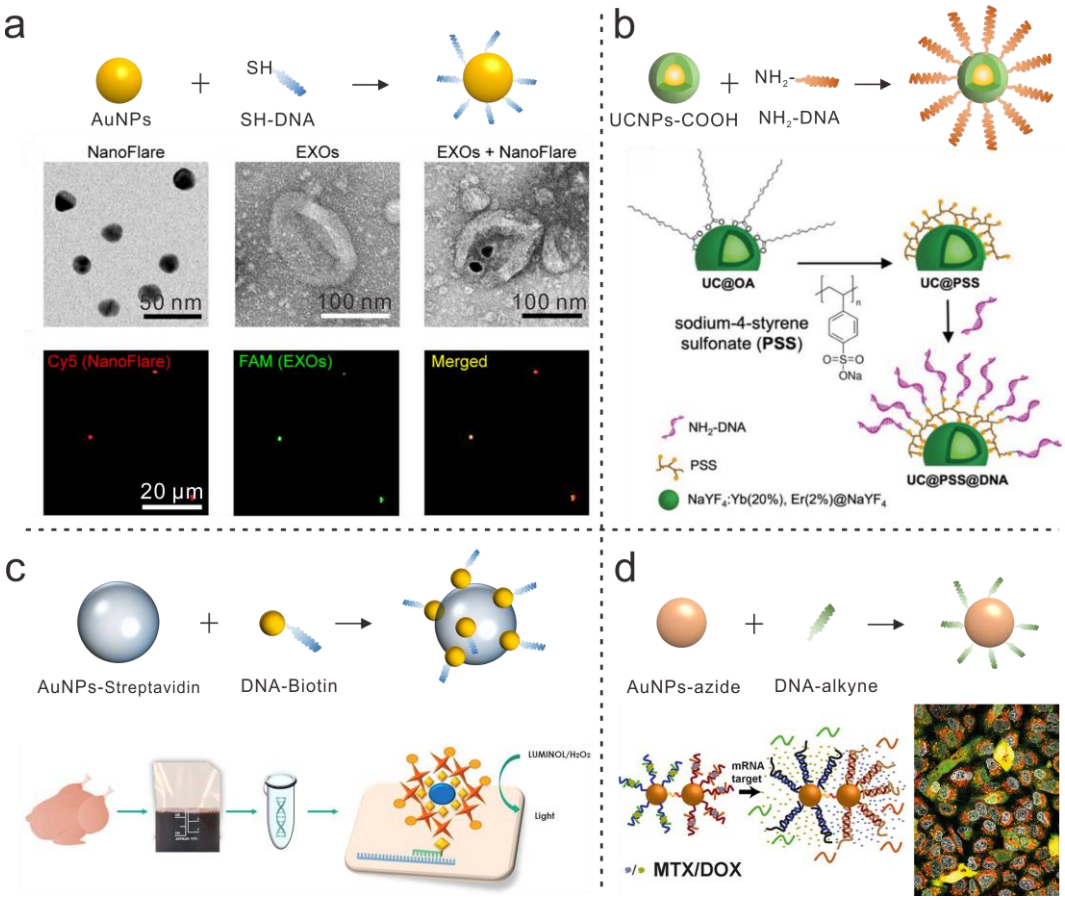

Figure 2. Schematic diagram of covalent bonding of DNA–nanoparticle conjugates. (**a**) Performance of nanoflares for miRNA detection and transportation of nanoflares into EXOs. Reproduced from Ref. [38] with permission. Copyright 2020 American Chemical Society. (**b**) Presentation of the UCNP-DNA bioconjugation in a schematic Reproduced from Ref. [43] with permission. Copyright 2022 Wiley-VCH GmbH. (**c**) Schematic diagram of the construction of biotinylated DNA and biotinylated nanoparticles connected by streptavidin to complete the sensor. Reproduced from Ref. [45] with permission. Copyright 2021 ELSEVIER. (**d**) Illustration of a multiplexed nanoparticle dimer that was joined via click chemistry using a DIBO-azide. Reproduced from Ref. [53] with permission. Copyright 2018 American Chemical Society.

Two DNA aptamer sequences are assembled on the surface of UCNPs by electrostatic adsorption, and the photoactivation ability of UCNPs is utilized to overcome the electrostatic adsorption and release the loaded two DNA aptamer strands after reaching a specific location, completing ultrasensitive imaging monitoring of single molecules on cell membranes (Figure 3a) [59]. Similarly, as shown in Figure 3b, aptamer DNA strands with redox activation ability can be electrostatically adsorbed on AuNPs with targeting ability to construct DNA–nanoparticle conjugates with gating effects that enable simultaneous spatial imaging of ATP and glutathione (GSH) in mitochondria [60]. This information is capable of being utilized to build pH probes with great temporal and spatial accuracy for tracking various physiological and pathological processes, which is equally crucial (Figure 3c) [61]. A variety of DNA sequences that have been detached from the nanoparticles and are reassembled into functional structures on their own can be loaded in addition to a single DNA sequence (Figure 3d). The sensitivity of DNA–nanoparticle conjugates for intracellular imaging monitoring of mRNA can be efficiently boosted with this technique [62]. All of the above work is illustrating the significance of interchangeable connections in biosensing applications.

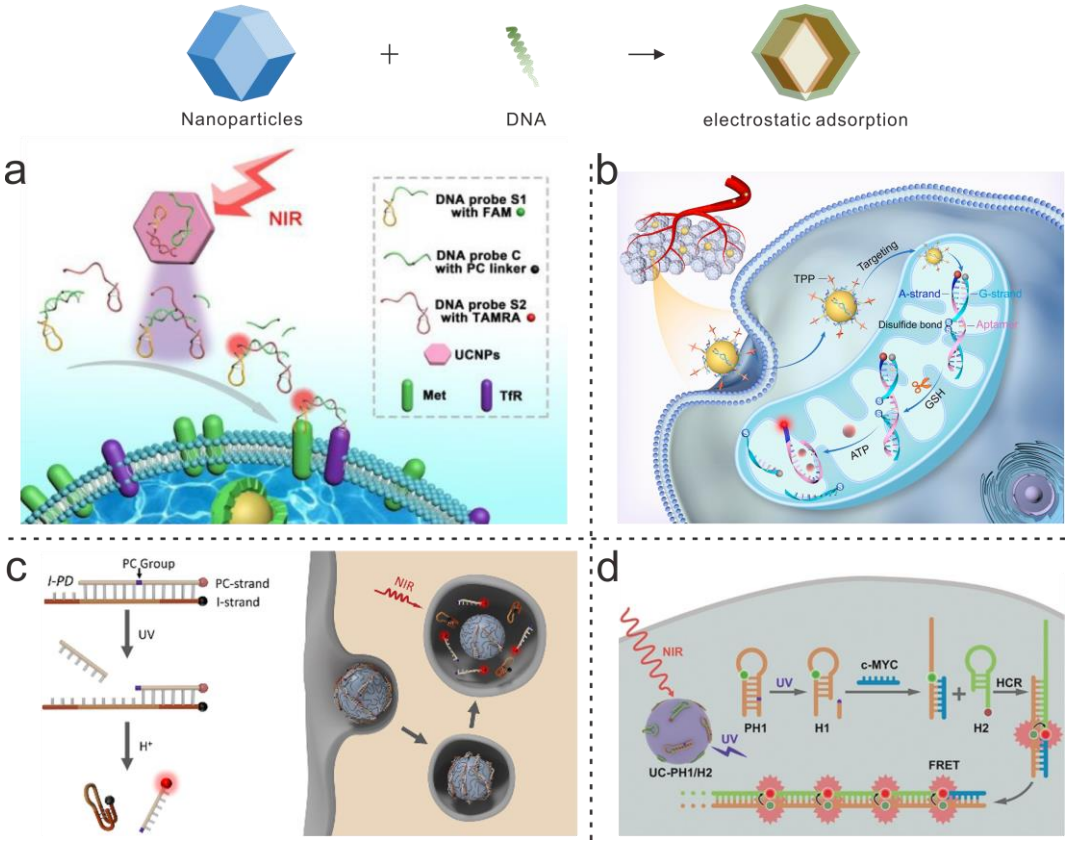

Figure 3. Schematic diagram of non-covalent bonding of DNA–nanoparticle conjugates. (**a**) A schematic illustration: DNA-UCNPs nanoprobes for detecting receptor dimers. Reproduced from Ref. [57] with permission. Copyright 2021 American Chemical Society. (**b**) Redox-activatable DNA nanodevice design schematic for AND-gated imaging of ATP and GSH in mitochondria. Reproduced from Ref. [58] with permission. Copyright 2021 American Chemical Society. (**c**) Diagram of the pH-sensing UV-activated DNA probe, I-PD. Reproduced from Ref. [59] with permission. Copyright 2020 American Chemical Society. (**d**) NIR light-initiated hybridization chain reaction (HCR) for spatiotemporally resolved mRNA imaging and signal amplification in living cells. Reproduced from Ref. [60] with permission. Copyright 2019 Wiley-VCH GmbH.

Notably, the triggering conditions for the above DNA–nanoparticle conjugates to work are diverse, including near-infrared light irradiation, pH stimulation, and the presence of a target, and all of these triggering effects are stronger than the force of electrostatic adsorption. Therefore, the conversion of functional switches can be successfully accomplished by taking advantage of the diverse and realistic physiological environment in organisms, as well as the strength of the forces acting, which is also a major advantage of non-covalent bond binding.

3. Biological Applications

This section will go over several notable applications of DNA–nanoparticle conjugates in biological and biomedical applications, such as sensing, bioimaging, and therapy (gene therapy, photothermal therapy, photodynamic therapy, and synergistic therapy). The link between functional DNA sequences and nanoparticles is highlighted in this section, with a focus on the personalized creation of DNA–nanoparticle conjugates with particular activities.

3.1. Biosensing

MicroRNAs (miRNAs) in mammalian cells can be imaged in situ spatiotemporally to reveal their structure and biological functions. The employing of DNA–nanoparticle conjugates as imaging tools for miRNAs in situ has tremendous potential. To achieve

intracellular miRNA imaging and accurate quantification in living cells without disrupting the cell membrane, some work has proposed a near-infrared (NIR) light-activated nanoprobe that can be utilized for highly sensitive in situ controllable miRNA imaging in living cells (Figure 4a). The NIR-activated nanoprobe employs a UCNP that acts as an NIR-UV sensor, triggering the following on the surface of the nanoparticle attached to the photocleavage of the dumbbell DNA probe. The structural alteration of the dumbbell probe induces a catalytic hairpin assembly of the target miRNA, through which an amplified fluorescence signal can be read in situ [63]. It is worth noting here that the photodegradable n-nitrobenzyl-protected DNA architecture is the architecture most extensively practiced as a functional DNA shell layer [64]. The same work successfully created an intelligent system based on NIR light-initiated DNA walkers for precise spatiotemporal regulation of living cells utilizing two DNA–nanoparticle conjugates (UCNPs and AuNPs) (Figure 4b). UCNPs are one of them, and they operate as DNA probe carriers, converting NIR into UV light to activate the precursor probes. Regarding high-resolution spatiotemporal imaging of intracellular miRNAs, AuNPs are employed as carriers of ATP-driven DNA walkers [65]. The device is exceedingly stable and has a very low fluorescence background. Meanwhile, it is highly desirable that DNA-based molecular circuits can perform complex information processing in biological systems. Li's group reports a conceptual approach to constructing photonic nanocircuits that enable DNA molecular computation with superior spatial accuracy in vitro and in vivo. Upon remote activation of spatially restricted NIR-light inputs, two cancer biomarker inputs, ATP and miRNA, can sequentially trigger conformational changes in the DNA circuit via structural switch aptamers and toe point-mediated strand exchange, leading to the release of signal output and the formation of more accurate in vivo imaging data of the organism [66]. Alternatively, multiple intracellular miRNAs can be exploited for simultaneous triggering, enabling spatially and temporally controlled on-demand precision imaging [67].

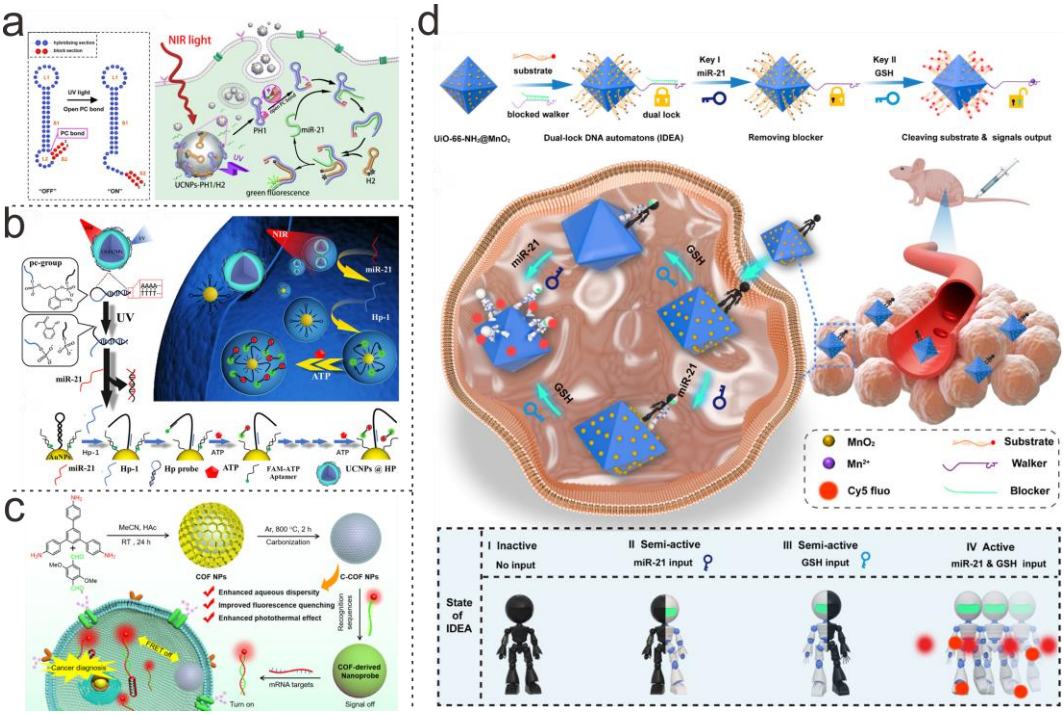

Figure 4. DNA–nanoparticle conjugates for biosensing applications. (**a**) The proposed controllable miRNA imaging nanoprobe's general principle. Reproduced from Ref. [63] with permission. Copyright 2020 American Chemical Society. (**b**) Schematic of the photoactivatable DNA walker system for

spatiotemporally resolved miRNA sensing. Reproduced from Ref. [65] with permission. Copyright 2021 American Chemical Society. (**c**) Schematic illustration of the preparation of carbonized COF-based nanoprobes for cancer cell imaging. Reproduced from Ref. [68] with permission. Copyright 2021 American Chemical Society. (**d**) Diagram of IDEAs for precise tumor imaging. Reproduced from Ref. [69] with permission. Copyright 2023 American Chemical Society.

In addition to UCNPs as carriers for DNA, covalent organic frameworks (COF) and MOF are also ideal core materials with excellent physicochemical properties. The work leads to the remarkable conclusion that carbonized COFs (C-COFs) can significantly improve the fluorescence burst efficiency and water stability of nanoscale COFs (Figure 4c). The probes prepared by the physisorption of dye-labeled DNA recognition sequences onto C-COFs for cell imaging can effectively illuminate biomarkers (survivin and TK1 mRNA) in living cells [68]. DNA-functionalized ZrMOF@MnO_2 exhibits a significantly enhanced fluorescence signal only when miRNA and GSH from tumor cells coexist, enabling accurate differentiation between tumor cells and healthy cells (Figure 4d) [69].

It is essential to involve a variety of enzymes in addition to miRNA, ATP, and GSH as regulatory molecules in the organism. An efficient type of DNA nanomachine was designed by utilizing two enzymes in the organism, telomerase (TE) and purine-free/pyrimidine-free endonuclease 1 (APE1) (Figure 5a). The walker of this nanomachine moves along a TE-regenerated trajectory, generating multiple amplified signals by which APE1 can be imaged in situ, providing a new paradigm for the development of more applicable and efficient DNA nanomachines [70]. In parallel, DNA–nanoparticle conjugates (E-SNAs) can be manipulated for nucleoplasmic translocation of proteins with cancer cell selectivity. E-SNAs are constructed by programmable design schemes, based on modules of aptamers that carry enzyme response units at pre-designed sites and are further combined with SNA nanotechnology (Figure 5b). E-SNAs are able to efficiently and specifically regulate the cytoplasmic–nuclear shuttle of RelA proteins, while remaining inactive in normal cells due to insufficient enzyme expression, thus accurately localizing the target protein within the cell [71]. The linkage pathway and applications of the DNA–nanoparticle conjugates from the above work are shown in Table 1.

Table 1. Summarizes the types of linkages and biosensing applications of DNA–nanoparticle conjugates.

DNA Structure	Nanoparticle's Type	Connection Type	Analyte	LOD	Application	Ref.
DNA dumbbell structure	UCNPs	Allotropic bond	miRNA-21	Single cell	In situ imaging	[62]
Hairpin DNA structure	UCNPs	Allotropic bond	miRNA-21	Single cell	In situ imaging	[64]
Double-stranded	UCNPs	Allotropic bond	ATP, miRNA-21	Single cell	In vivo imaging	[65]
Triangle structure	UCNPs	Allotropic bond	miRNA-21, miRNA-373, miRNA-155	Single cell	In situ imaging	[66]
Single strand	COFs	Electrostatic adsorption	mRNA	Single cell	Cancer diagnosis	[67]
Double-strands	ZrMOF@MnO_2	Covalent bonding	miRNA-21, GSH	Single cell	In vivo imaging	[68]
Double-Strands	AuNPs	Covalent bonding	RelA protein	Single cell	In situ imaging	[69]
Double-Strands	AuNPs	Covalent bonding	APE1 enzyme	Single cell	In situ imaging	[70]

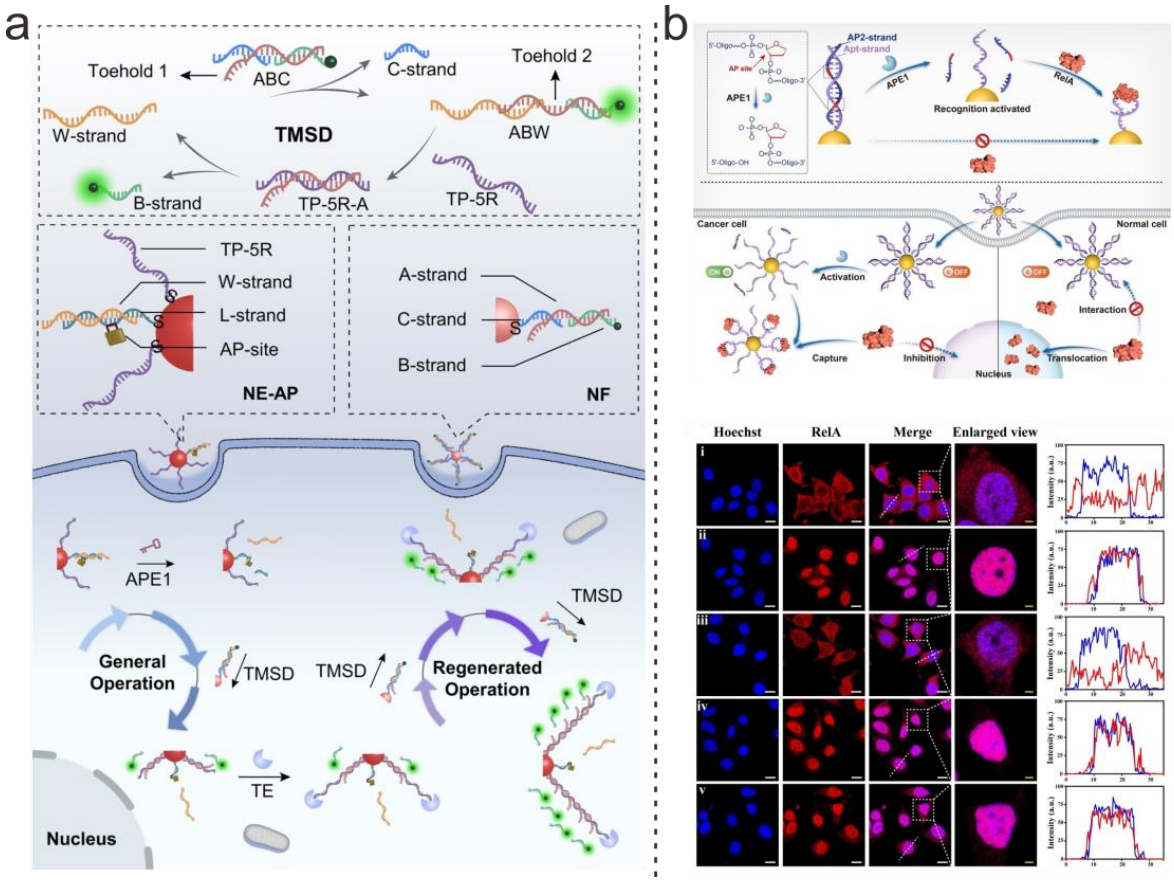

Figure 5. (**a**) Diagram of the TE-activatable regenerative DNA nanomachine (NEAP/NF) for sensing of intracellular APE1. Reproduced from Ref. [70] with permission. Copyright 2023 Wiley-VCH GmbH. (**b**) Design of the enzyme-operated SNA (E-SNA) for cancer cell-selective regulation of cytoplasmic-to-nuclear translocation of RelA protein. Scale bar, 2 μm. Reproduced from Ref. [71] with permission. Copyright 2023 Wiley-VCH GmbH.

3.2. Biomedical

Precise application of DNA–nanoparticle conjugates for imaging targets in living organisms is a prerequisite for accurate biomedical treatment [72–75]. The introduction of small interfering RNA (siRNA) in the DNA shell layer is an effective therapeutic approach to regulate the expression of target genes. The multifunctional three-dimensional (3D) DNA shell contains a degradation-resistant Y-shaped backbone (hardened triangular sticky DNA brick) and is programmed to lay flat on the siRNA-packed AuNPs. After the alignment of the aptamer on the outer surface, siRNA-encapsulated DNA–nanoparticle conjugates with excellent biocompatibility are obtained, siRNA/Ap-CS. In this, the siRNA is internally encapsulated in the 3D DNA shell, ensuring that it is not degraded by the enzymes in the outermost layer of the 3D DNA shell (Figure 6a). The conjugate-loaded siRNA can be released by endogenous miRNA and gene silencing in tumor cells, leading to apoptosis and enabling gene therapy [76]. Next, a freshly developed approach utilizes a simple, versatile, and inexpensive platform (AuNPs-DNA) to control the release of cholesterol-coupled oligonucleotides [77]. Nanoclusters formed by AuNPs-DNA combine the platform into a dual-release system that allows the delivery of a hydrophobic drug with zero-order kinetics followed by the rapid release of cholesterol-coupled DNA for therapeutic purposes and holds promise for future applications in downregulating the expression of b-galactosidase in *E. coli* (Figure 6b).

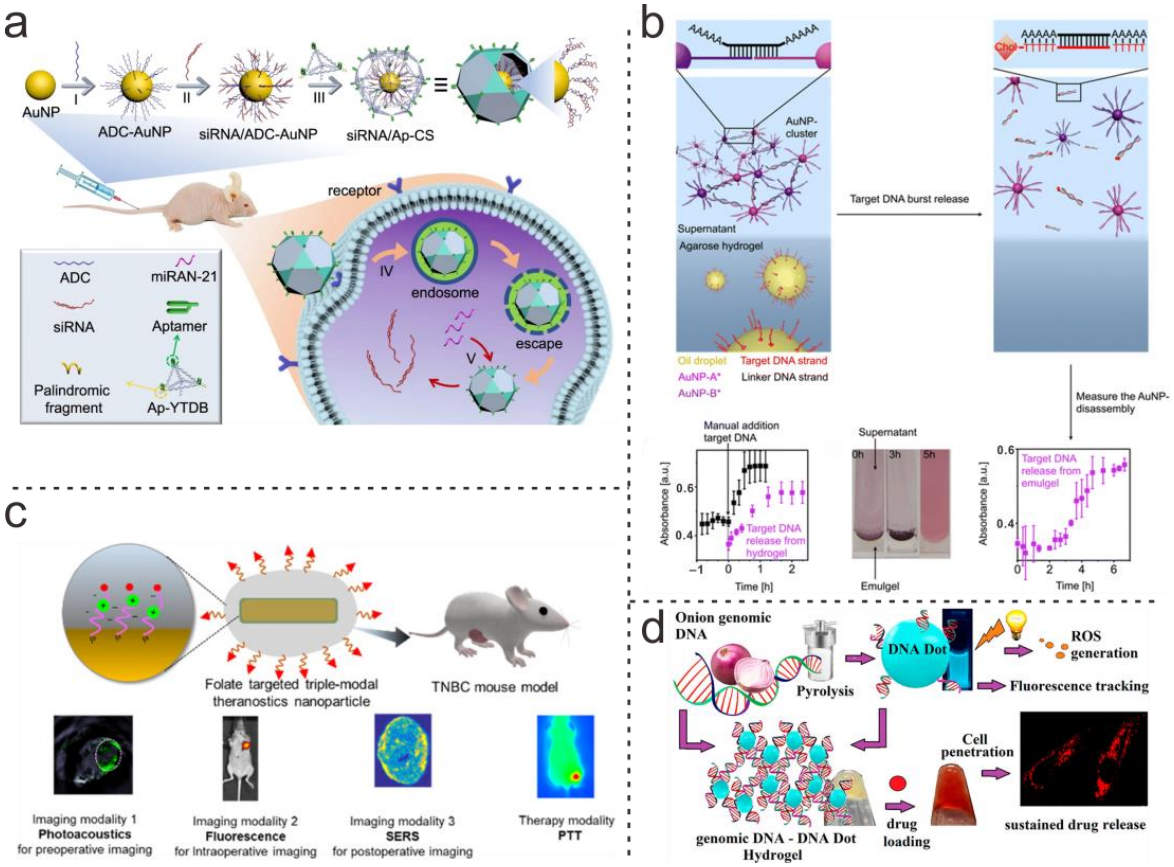

Figure 6. DNA–nanoparticle conjugates for biomedical applications. (**a**) Building a gold nanoparticle with a multi-purpose 3D DNA self-assembled multilayer core/shell nanostructure (siRNA/Ap-CS) and employing it to deliver siRNA to tumor cells with precision and control their release. Reproduced from Ref. [76] with permission. Copyright 2021 Nature. (**b**) Schematic of the DNA-AuNP-system and the disassembly of AuNP aggregates induced manually and by releasing the target DNA. Reproduced from Ref. [77] with permission. Copyright 2021 Nature. (**c**) Schematic representation of a TMNP and different optical imaging and therapy modalities offered by the TMNPs for in vivo applications. Reproduced from Ref. [78] with permission. Copyright 2022 American Chemical Society. (**d**) Schematic of synthesis and in vivo application of DNA hydrogel. Reproduced from Ref. [79] with permission. Copyright 2023 American Chemical Society.

For in vivo imaging and treatment of organisms, such as triple-negative breast cancer, early and precise identification, and treatment is critical for better disease management and increased life expectancy. On the basis of these needs, innovative biocompatible tri-modal nanoprobes (TMNPs) provide optical imaging employing photoacoustic, fluorescence, and surface-enhanced Raman scattering (SERS), as well as photothermal therapy (PTT) exploiting near-infrared (NIR) light [78]. Based on the modifiability of DNA, positively charged NIR fluorophores were designed and screened to obtain optimal fluorescence emission and SERS signals. As seen in the experimental results, selective exposure of tumors to the NIR laser showed effective thermal tissue ablation without causing systemic toxicity, creating a treatment platform with excellent imaging–treatment integration (Figure 6c). In addition to synthetic inorganic nanoparticles as carriers, plant-sourced DNA–nanoparticles (DNA dots) created from onion genomic DNA (gDNA) are without any chemicals and exhibit superior biocompatibility (Figure 6d). DNA dots further form stimuli-responsive hydrogels with multifunctional properties by self-assembly with hybridization-mediated precursor gDNA. Its main functional type of strand is contributed by surface-suspended DNA strands resulting from incomplete carbonization during annealing. DNA dot hybrid hydrogels proved to be an excellent drug delivery vehicle for on-demand reactions by

tracking slow release through the intrinsic fluorescence of DNA dots and by normal visible light photoexcitation [79]. The linkage pathway and applications of the DNA–nanoparticle conjugates from the above work are shown in Table 2.

Table 2. Summarizes the types of linkages and biomedical applications of DNA–nanoparticle conjugates.

DNA Structure	Nanoparticle's Type	Connection Type	Treatment Modalities	Application	Ref.
Y-shaped backbone-rigidified triangular DNA	AuNPs	Covalent bonding	Gene silencing	Cancer therapy	[75]
Cholesterol-conjugated DNA	AuNPs	Conjugate connection	Gene silencing	Drug release calculation	[76]
Single DNA	AuNRs	Covalent bonding	Phototherapy	Triple-negative breast cancer therapy	[77]
Biomass DNA	DNA dots	Conjugate connection	Photoactivated ROS Generation	Cancer therapy	[78]

4. Conclusions and Outlook

DNA–nanoparticle conjugates have attracted widespread attention in biosensing, bioimaging, drug delivery, and photoactivated biotherapeutics due to their high water solubility, functionalized surface modifications, and excellent physicochemical properties. In this review, we summarize the various assembly principles of DNA–nanoparticle conjugates and the recent research progress in the fields of bioimaging, photothermal, photodynamic therapy, gene therapy, etc. Although DNA–nanoparticle conjugates have made great progress in these aspects, many problems still exist in practical applications: (1) The broadest functional DNA sequences currently screened and applied include DNA aptamers and DNAzyme, followed by complex DNA structures introduced for the purpose of signal amplification, such as HCR, catalytic hairpin assembly (CHA), Y-types, and other steric structures. The aforementioned functional DNAs can be applied in a variety of biomedical fields; therefore, designing and screening more kinds of functional DNA sequences is an effective means to develop novel DNA–nanoparticle conjugates and expand their applications; (2) Exploring more diverse methods of surface modification of nanoparticles and assembling multiple types of functionalized DNA sequences on them. It is expected that the physicochemical properties of the abundant nanocarriers can be fully utilized to organically combine them with functionalized DNA to achieve the accumulation of dual functions and maximize the synergistic functions; (3) To develop more types of DNA shell layer and nanoparticle binding methods, and to introduce more abundant and on-demand controlled covalent bonding modes into the conjugate binding to form more diversified and stable DNA–nanoparticle conjugates. We believe that the successive development of DNA–nanoparticle conjugates based on the above-mentioned richer species will lead to breakthroughs in solving major problems in biosensing and biomedical fields, benefiting more research fields in the near future.

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